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CROHN'S DISEASE: A CHALLENGE TO THE ENTITY CONCEPT

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INTRODUCTION

In 1932, Crohn and his colleagues published their classic paper entitled "Regional ileitis. a pathologic and clinical entity" (1).

Preoccupation with etiology has been the incentive for a large number of studies aimed at identifying the causative agent of Crohn's disease. Knowledge of etiology and pathogenesis, it was felt, was crucial to the development and application of relevant and successful therapy. A vast amount of literature ensued which focused on the etiopathogenesis of the disease. In contrast, only few papers have been published which deal with the other element in Crohn's original work, i.e. the entity hypothesis.

After more than 5 decades of intensive clinical and basic research, no single etiology for Crohn's disease has emerged, and proposed etiologic factors typically appear to apply to a small proportion of Crohn's patients only. Moreover, clinical and pathological scrutinies during these years have revealed that the functional morphologic lesions of the disease are by no means specific, but rather represent a spectrum of phenotypic manifestations. The diagnosis of a fair proportion of these protean manifestations remains equivocal. These considerations prompt to step back and seriously contemplate the possibility that Crohn's disease might not be a disease entity (2-4).

If Crohn's disease were not a disease entity with regard to etiology, but a heterogeneous disorder, this would imply that more than one etiologic mechanism could lead to the clinico-pathologic syndrome which we call Crohn's disease (5, 6).

It Is the purpose of this paper to discuss a number of theoretic nosological arguments with respect to the entity concept of Crohn's disease. Since it will be shown that it is quite conceivable that a single or simple etiology does not exist we will suggest breaking with the dogma that Crohn's disease is a disease entity. Arguments to support this hypothesis will be derived from:

1) the heterogeneous appearance of the disease in the patient population,
2) the insufficient and unsatisfactory etiologic mechanisms proposed, and, on a different level of discussion, from
3) a more fundamental analysis of the usefulness of classifying diseases according to their etiology.

1. Phenotypic (clinico-pathologic) heterogeneity

To most clinicians, the qualitative picture of a typical Crohn patient appears to be uncontroversial, but a considerable proportion of cases does not exactly meet the criteria because the symptoms and signs, whether clinical, radiological or patho-morphological, may vary substantially in extent and intensity. For instance, conclusive diagnostic value is usually attached to the finding of granulomas on histopathological examination. However, these occur in only about 60% of the patients (7). Ironically, Crohn himself stated that the granulomas were most likely accidental secondary findings and not an essential feature of the pathologic changes (1). A clear-cut defining characteristic (8), with which to demarcate "Crohn's disease patients" from among the heterogeneous population with inflammatory bowel phenotype that remains after the diseases with known etiopathogenesis, either infectious or non infectious, have been excluded, does not exist. One of the difficulties in conducting epidemiological studies of Crohn's disease is the apparent variability in diagnostic criteria and nomenclature over time and among different clinical centers (9).This heterogeneity of disease appearance and the apparently factual impossibility to define adequate diagnostic criteria, joined to the large amount of time that is often needed, after the onset of symptoms, to eventually decide on the diagnosis, may indicate that we are actually not dealing with one disease entity.

2. Absence of a single etiological agent

An amazingly wide variety of extrinsic and intrinsic etiologic factors has been proposed, which includes physical (trauma), chemical (oral contraceptives), dietary (processed fats, refined sugar). biotic (viruses, enteric flora, mycobacteria), genetic (defective complement system, increased intestinal permeability), immunopathologic (neutrophil dysfunction, autoimmunity, immunoregulatory disturbance), psychogenic and behavioral (smoking) agents. Of the several etiopathogenetic hypotheses and the many etiologic agents only few survive as likely ones today (10-12). Not only could the causative association of most of these agents with Crohn's disease not be confirmed in other studies, but many of the proposed etiologic factors were found in a disappointingly limited proportion of the Crohn patients. For example, a proposed complement dysfunction was identified in only 8 of 21 Crohn patients (13), and a strain of likely causative mycobacteria in only 3 of 14 patients (14). Furthermore, although increased intestinal permeability as an etiologic factor was clearly supported by a statistically significant increase in the mean permeability of Crohn patients versus controls, at least 5 of the 11 Crohn patients studied has a permeability value well within the control range (15). This does not justify the opinion that any one of these constitutes the principle causative element of the disease.

A variety of alternatively possible causal sequences could lead to the phenotypic syndrome we call Crohn's disease. In this view, Crohn's disease constitutes a particular basic reaction pattern, a certain type of host response (3), which the digestive tract may express upon interaction with a number of noxious agents. The population of Crohn patients then includes several etiological groups, differing with respect to the initial causation, but more or less similar as to the eventual phenotypic disorder for which medical help is sought. Indeed, Crohn's disease does not have the characteristics of a single cause, either extrinsic or intrinsic (3,4) which implies that an abnormality present in only a minority of patients could still have a causative role (5), and be of major therapeutic significance for the patient concerned.

3. The disease entity concept

Up to this point, the expression "disease entity" was used with the tacit assumption that disease entities are in fact etiological entities, i.e. every disease has or should have its own etiology. Certainly, in contemporary medicine we adhere to the principle that diseases ought to be defined and classified according to their etiology. This implicit axiom, however, is not as self-evident as it seems, and when one tries to define the essence of disorders like Crohn's disease, one inevitably stumbles over it. After all, what is the use of formulating disease entities?

For certain diseases, the causality concept does not seem accurate for defining disease categories end for designing therapeutic intervention and management. These diseases are considered to have a complex etiology. They are so-called multifactorial disorders. For these diseases to develop, a concerted action of extrinsic environmental and intrinsic hereditary factors appears to be necessary. Even if some of the originally eliciting factors were known, management of a patient would primarily depend on type, grade and stage of the particular disease pattern. This requires a classification system based on prognosis rather than on etiology.

In an excellent essay, Feinstein (16) argues that "functional consequences in the severity of disease, rather than its pathologic essence, are usually the reasons why most patients are treated or hospitalized", but that prognosis has been given relatively little scientific attention. Our current, etiology-based, conceptual model yields diagnoses which reflect a single and static aspect of the patient, and no dynamic anticipation of a future disease course. He strongly recommends the development of a specific taxonomy to standardize the names and to categorize the severity of disorders, based on a scientific classification system of functional severity. This he considers the main intellectual challenge for clinicians today.

With respect to Crohn's disease, studies such as the one by Holdstock and colleagues (17) are of prime importance. They showed that there were very few differences in disease course between patients with Crohn's disease of the colon and those with ulcerative colitis. From a prognostic point of view, both diseases are remarkably similar. Yet, the label "Crohn's disease" still symbolized a poorer prognosis, apparently unwarranted, and the pharmacological treatment Crohn patients usually receive is

different from that of patients with ulcerative colitis. Dworken (18) raised the issue "whether distinguishing between Crohn disease and ulcerative colitis should be an end in itself. Indeed, why impose a dichotomous classification at all?".

In conclusion, to consider Crohn's disease a disease entity is not very useful from a prognostic point of view. Successful patient management is probably more in need of a scientifically sound classification system according to disease severity than of the speculative search for a unifying etiology.

PRACTICAL CONSEQUENCES OF ADOPTING A NEW APPROACH

Although it is commonly accepted that intrinsic as well as extrinsic factors are needed for the disease to develop, the relative importance of both elements, their identity and whether they are involved in the onset (etiology) or in the further development (pathogenesis) of the disorder is largely unknown. Positive identification of any etiopathogenic factor may be of much relevance to the management of the specific subgroup of Crohn patients which develop the disease as a result of that particular factor.

This view would, therefore, have an impact on therapy, as one group of patients might need a different therapeutic approach from another group, according to the relevant etiologic factor involved in each one.

Patients and their relatives may be examined for the expression of certain defects that are conceivable involved in the etiopathogenesis (19). Such defects notable include a potentially defective barrier function of the intestine (20), and dysfunctions of the acute inflammatory reaction which might compel the body to switch to a proliferative granulomatous response in order to deal with the noxious agent (21).

As mentioned above, what is called Crohn's disease is a more or less isomorphic constellation or a syndrome of coherent functional and morphologic lesions, which presumably reflects a basic response pattern of the gastrointestinal tract to more than one eliciting agent (22). The eventual histopathological presentation of the disease is probably mediated through specific dysregulated immunopathologic processes which may be triggered by nonspecific agents (23).

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